CERTIFICATE OF ELECTRONIC SUBMISSION

September 20, 2006

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Runge et al.	Group Art Unit: 1634
Serial No.: 09/832,069	Examiner: Goldberg, Jeanine Anne
Filed: April 10, 2001	Atty. Dkt. No.: CLFR:183US
For: Mitochondrial DNA Damage as a Predictor of Coronary Atherosclerotic Heart Disease	

REPLY BRIEF

MS Appeal Briefs
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Appellants hereby submit this Reply Brief to the Board of Patent Appeals and Interferences pursuant to 37 C.F.R. §41.41. Based on the mailing date of the Examiner's Answer July 25, 2006, this Reply Brief is due September 25, 2006. Thus, the filing of the present Appeal Brief is timely. It is believed that no fees are due, however, if any fees are due for any reason relating to the enclosed materials, the Commissioner is authorized to deduct said fees from Fulbright & Jaworski L.L.P. Account No.: 50-1212/CLFR:183US.

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I. Rejection of claims 6 and 16-20 as lacking enablement under 35 U.S.C. §112, first paragraph

The Answer maintains the rejection of claims 9 and 16-20, alleging that these claims are not enabled by the specification, for reasons of record. Principally speaking, the Action takes the position that Appellant's specification fails to provide sufficient evidence that, for example in the case of rejected claim 16, mitochondrial mRNA production can be used to measure the "amount" of mtDNA damage. We continue to maintain, for the reasons reviewed in our opening Appeal Brief and summarized herein, that the Examiner has failed to set forth a *prima facie* case of non-enablement of claims 6 and 16-20.

First of all, the Answer fails to point to any cognizable *evidence* of non-enablement – evidence that supports the Examiner's questioning of the objective truth of Appellant's assertions. The Answer's main point appears to be that the *Appellant's* have allegedly not shown a correlation between, for example, mitochondrial mRNA ("mtRNA") production and an amount of mitochondrial DNA ("mtDNA") damage. While we disagree with the underlying premise that Appellant's specification does not provide evidence of enablement (see below), we point out that it is the Examiner who bears the burden of making out the *prima facie* case of non-enablement. Notably, none of the references cited by the Examiner provides any suggestion whatsoever that the Examiner can point to that supports a conclusion of non-enablement.

In fact, for reasons stated in our opening Brief, if anything, the evidence relied upon by the Examiner supports the opposite conclusion. For example, we provided evidence that the Corral-Debrinski *et al.* article indicates a correlation between the amount of mtDNA damage and the mRNA readouts of genes such as the OXPHOS gene. In the Answer, although not clearly

stated, the Examiner has apparently responded that the correlation in Corral-Debrinski *et al.* is between mtDNA damage and "nuclear" OXPHOS gene expression. This is not true. As can be seen from the statement that:

> We have examined this hypothesis by analyzing the levels of the common 4977 nucleotide pair (np) mtDNA deletion ($mtDNA^{4977}$), and the ***transcript levels*** of nDNA ***and mtDNA OXPHOS*** genes in normal and coronary atherosclerotic hearts of various ages.

Corral-Debrinski, page 171, col. 2 (emphasis ours). From these studies, the authors conclude that:

> Consistent with this concept, both our previous study (Corral-Debrinski *et al.*, 1991) and the current work have shown that CAHD is associated with dramatically elevated mtDNA damage and the concomitant ***induction of OXPHOS gene transcripts***.

Id. at page 177, col. 2 (emphasis ours). Thus, it is evident from this that Corral-Debrinski et al. recognizes a correlation between mtDNA damage and the level of *expression* of "mtDNA oxphos genes.

Furthermore, Appellants have come forward with strong evidence that the art does recognize a correlation between, for example, mtRNA expression and the amount of mtDNA damage. This is reviewed at the top of page 7 of the opening Brief. The Examiner responds to our reference to Lenaz by stating that Lenaz "does not provide any guidance into ***how*** the mtDNA encoded protein is indicative of oxidative stress in an individual, as required by the instant claims." Answer at 10 (emphasis ours). Applicants would merely note that the Examiner does not question that Lenaz teaches a correlation between mtDNA damage and oxidative stress protein production (see, for example, Fig. 2, page 56, of Lenaz which postulates

a correlation between mtDNA mutations and "defective mtDNA-encoded proteins" and "defective electron transfer"). Rather, the Examiner is inappropriately requiring an explanation in the reference as to the underlying theory of the invention. However, this is an inappropriate standard. *Diamond Rubber Co. v. Consolidated Rubber Tire Co.*, 220 U.S. 428, 435-36 (1911) ("[a]n inventor need not know the why of the scientific and technologic principles underlying an invention."); see also *In re Isaacs and Lindenman*, 146 U.S.P.Q. 193, 197 (CCPA 1965) ("[a]n applicant need not understand the theory or scientific principle underlying his invention.")

The Examiner similarly states that Williams et al. and Hudson et al. do not "contain information regarding detecting mtDNA damage by measuring mitochondrial mRNA production" *etc.* See Answer, bottom of page 10, top of page 11. While Applicants believed that this evidence was apparent, we will type it in here directly:

> The reduction in MnSOD activity in *Sod2* $^{-/+}$ mice was correlated to an increase in oxidative damage to mitochondria: decreased activities of the Fe-S proteins (aconitase and NADH oxidoreductase), increased carbonyl groups in proteins, and increase levels of 8-hy-droxydeoxyguanosine in mitochondrial DNA.

Williams *et al*, Abstract, page 28510.

> Previous reports from this lab have shown a decrease in mitochondiral cytochrome c oxidase (COX) activity associated with a reduction in COX gene and protein expression and a similar decrease in the rate of mitochondrial protein synthesis. Damage to mitochondrial DNA may contribute to this decline.

Hudson *et al.*, first paragraph, page 573.

Note, we are not at all agreeing that these references "teach" or "suggest" the invention – as the Examiner appears to be of the opinion must be shown – all we are saying is that these references support a conclusion that there is a correlation between mtDNA damage and mtRNA, mt protein expression, *etc.*

Lastly, the Examiner appears to disregard the evidence of enablement from Appellant's specification. In Appellant's opening brief, specific examples of correlations between the amount of mtDNA damage and, for example, mtRNA expression, is set forth. We have been unable to find any comments from the Examiner that address the specific teachings in the specification that were pointed to in the opening Brief, and we would refer the Board to our opening Brief at page 8. Since we believe that this evidence is irrefutable, for the Board's convenience we will simply reproduce our opening argument here:

> Nevertheless, we disagree that with the Examiner's position that there is no exemplary support in the specification. We would, for example, direct the Board's attention to Example 5 of the specification, pages 35-37 and Figure 3, which demonstrates the use of Northern transcript analysis to quantify mitochondrial mtRNA transcript levels (claim 16). These studies are discussed in Example 9, at page 44, lines 5-18, and demonstrate a correlation between ND2 and cyt b transcript levels with peroxynitrite treatment. Similarly, with respect to protein production as a measurement of mt DNA damage (claim 17), the Board is directed to Example 6, pages 37-38, which demonstrates an assessment of mitochondrial protein synthesis as a measure of oxidative damage, and provides a reference for exemplary analyses. Similarly, Example 7, pages 38-39, demonstrates assessing oxidative damage by measuring changes is mitochondrial oxidative phosphorylation (claim 18) or mitochondrial ATP production (claim 19), and Example 9, pages 40-48, demonstrate assessing oxidative damage as a function of mitochondrial redox state (claim 20). The significance of the foregoing studies as a measurement of oxidative damage are explained and discussed in Example 9.

For the foregoing reasons, and as set forth in our opening Brief, the Board is requested to overturn the Examiner's rejection.

II. A rejection of claims 6, 8-9 and 14-23 as indefinite under 35 U.S.C. §112, second paragraph

Appellants do not entirely understand the Section 112, second paragraph, rejection. At page 8 of the Answer, it is stated that the rejection is because "it is unclear whether the final

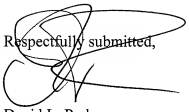
clause of the method is directed to detecting amount of damage or mere presence of damage. The claim states, 'wherein such damage is indicative of oxidative stress in said individual.' Thus, the claims does not particularly appear to require establishing a correlation based upon any amount or ratio or other measurement of quantity of damage."

This rejection is unclear in that, contrary to the Examiner's statement, claim 6 does not recite "wherein such damage is indicative of oxidative stress in said individual," it instead recites "wherein such ***amount*** of damage is indicative of oxidative stress in said individual." Thus, it is clear from a direct reading of the claim that an "amount" of damage is what is claimed.

Now, for the first time in the Answer, the Examiner appears to instead be suggesting that Applicants are required to place some *operable parameters* into the claims in the form of a correlation between quantity of damage and the amount of oxidative stress, then such a requirement is clearly contrary to the caselaw. The Board is referred to *In re Johnson*, 558 F.2d 1008, 194 U.S.P.Q. 187 (CCPA 1977) and *Ex parte Jackson*, 217 U.S.P.Q. 804 (BPAI 1982). These cases stand for the proposition that for the purposes of section 112, *second* paragraph, it is the function of the specification, and not the claims, to set forth operable parameters. There are a number of similar holdings. In this regard, it is perhaps noteworthy that the Examiner has found that claims 8-9, 14-15 and 21-23 to be fully enabled by the specification, yet these claims have been rejected under section 112, second paragraph.

Accordingly, the Board is requested to overturn the Examiner's rejection of the claims on the basis of section 112, second paragraph.

Respectfully submitted,



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